

Remarks

Claims 1-20, 22-23, and 26-40 are currently pending in the present application and remain rejected under 35 USC 103(a). Applicant has submitted the present amendment and response in conjunction with a request for continued examination. Applicant respectfully requests reconsideration of the claims as amended, and further in view of the discussion set forth below.

Applicant has inserted into the specification a paragraph which recites particular salts of compounds of the present invention. With this amendment, Applicant wishes to bring the description in the specification into conformance with the claims. Basis for the salts recited in this paragraph may be found in original claims 10, 12, 14, 16, and 18, thus, it is believed that the insertion of this paragraph involves no new matter.

Applicant has identified errors that appear in the description of the protocol for the "Bioavailability in Rats" portion of the "Pharmacological Results" section of the specification. (Note, however, that the heading above Table 2 on page 19 is correct and was underscored in the specification as originally filed.) With the present amendment to the Pharmacological Results section, Applicant wishes to delete the erroneous text from the specification. As the amendment merely involves deletion of erroneous text, it is believed this amendment to the specification involves no new matter.

Applicant has provided new claims 41-60 to replace the set of claims currently on file. The amended claims are being provided in order to more particularly claim the subject matter of the present invention or to reduce the number of pending claims through use of dependent claim formats. Bases for the new claims may be found in the specification, including the original claims, and as well as the amendments previously submitted on May 3, 2006. For example, basis for claim 41 may be found in original claim 2 as well as the specific compound examples provided in the specification (e.g esters wherein $R = C_2-C_{10}$ alkyl). Basis for new claim 42 may be found in original claim 3; bases for new claims 43-47 may be found in original claims 4-8; basis for new claim 48 may be found in original claims 10, 12, 14, 16, and 18; bases for new claims 49-53 may be found in original claims 9, 11, 13, 15, 17 which specifically provide for the esters "or" pharmaceutically acceptable salts. Basis for new claim 54 may be found in the specification at page 12 of the specification which describes the general synthesis procedures of Scheme I ("The product is then isolated and purified using techniques well known to one of ordinary skill in the art . . .") Bases for new claims 55-60 may be found in the original claims 20, 22 (previously amended), 23

(previously amended), and previously submitted claims 26-40, as well as the basis provided in the specification and original claims for compounds wherein R = C₁-C₁₀ alkyl.

As the above amendments are being provided to bring the specification and claims into conformance, or to delete erroneous text from the specification, or to more particularly claim the subject matter of the present invention, Applicant respectfully submits that said amendments do not encompass new matter. Applicant courteously requests entry of the presently submitted amendments.

The claims of the present invention remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Salhoff *et al.*, in view of Bundgaard (WO88/01615) (Bundgaard I). The stated objective of the present invention is to provide monoesters of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid which provide improved bioavailability of the parent monoacid in a patient. (U.S. Patent Application 10/511,452, page 1, line 17-19) Further, as presently amended, the instant invention is specifically drawn to monoester prodrugs bearing a C₁-C₁₀alkyl group (or C₂-C₁₀alkyl) on the carboxyl residue at the 3-position of the decahydroisoquinoline core. Applicant respectfully maintains that rejection of the present claims is inappropriate on the ground that the Examiner has failed to establish that the subject matter of the present invention is *prima facie* obvious in light of the cited art.

As noted by the Examiner, the *Graham* factual inquiries, including (1) determining the scope and content of the prior art and (2) ascertaining the differences between the prior art and the claims at issue, are applied in establishing a background for determining obviousness under 35 USC 103. Faced with this background, however, the burden remains on the Patent Office to show a *prima facie* case of obviousness, which requires: suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; a reasonable expectation of success; and a teaching or suggestion of all claim limitations. M.P.E.P. §2143.

Salhoff *et al.* discloses *in vitro* and *in vivo* pharmacology for (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid. Bundgaard I discloses that carboxylic acid-derivative drugs are characterized by poor absorption, and thus poor bioavailability, as a result of ionization of the carboxylic functional group when exposed to physiological pH. Bundgaard I generally discloses a variety of approaches that have been employed in an attempt to improve the bioavailability characteristics of carboxylic acid drugs, including

aliphatic esters, aromatic esters, acyloxyalkyl double esters, and alkoxycarbonyloxyalkyl double esters. However, Bundgaard I only specifically exemplifies highly functionalized esters comprising an (N,N-disubstituted-amido)alkyl moiety as a means for improving the bioavailability of carboxylic acid-derivative drugs.

As noted by the Examiner, Salhoff expressly does not teach the ester of the carboxyl residue at the three position of the decahydroisoquinoline core. (Official Action, date February 3, 2006) The Examiner thus relies upon Bundgaard I as allegedly teaching any and all ester prodrug formulations. (Official Action, date July 25, 2006) However, a fair reading of Bundgaard I actually refutes the Examiner's position. Regarding simple alkyl esters of the type of the present invention, Bundgaard explicitly states:

several aliphatic or aromatic esters of carboxylic acid drugs are not sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example simple alkyl and aryl esters of penicillins are not hydrolyzed to active free penicillin acid in vivo. . . and therefore have no therapeutic potential . . . Similarly, the much reduced anti-inflammatory activity observed for the methyl or ethyl esters of naproxen . . . and fenbufen . . . relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo. . . . Pentopril is another ethyl ester prodrug of an angiotensin-converting enzyme inhibitor which also is highly stable in human plasma. In this case less than 50% of an oral dose of the prodrug appears to be deesterified to the active parent acid.

WO 88/01615 (page 2, line 18 through page 3, line 9)(citations omitted)

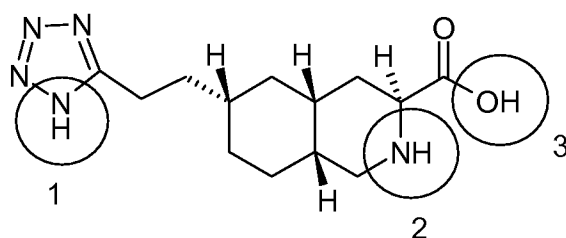
Far from providing the requisite suggestion or motivation to prepare the simple alkyl esters of the present invention, it is Applicant's view that Bundgaard I actually teaches away from the present invention. Combining the reference teachings of Salhoff with those of Bundgaard I would not lead to the esters of the present invention, but rather the highly functionalized esters comprising an (N,N-disubstituted-amido)alkyl moiety. Furthermore, in view of the express teachings of Bundgaard I that such esters are not sufficiently labile in vivo, even if one skilled in the art were to proceed with the preparation of simple alkyl esters of the type of the present invention, there would be no reasonable expectation that such esters would improve the bioavailability of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

In view of the failure of Bundgaard I to teach simple alkyl esters, the Examiner cites, in the present Official Action, Wang *et al.*, *Curr. Med. Chem.*, 4, 437-453(2000) (Wang) and Bundgaard *et al.*, *J. Med. Chem.*, 28(8): 979-981(1985) (Bundgaard II) apparently for the proposition that the motivation to prepare simple alkyl esters of the

type of the present invention was within the knowledge generally available to those of ordinary skill in the art.

Wang discloses a variety of prodrug approaches that have been employed for the purpose of increasing the oral activity of RGD peptidomimetic analogs. Among those disclosed in Wang are simple alkyl (e.g methyl and ethyl) esters, double amidoxime ester prodrugs, double carbamoyl ethyl ester prodrugs, triple prodrugs (acetate-carbamoyl-alkyl esters; carbamoyl-dialkyl esters; and hydroxyl-dialkyl esters), and coumarin based cyclic prodrugs. However, Wang further discloses that the difficulty in developing orally active RGD analogs stems in part from the intrinsic need for such molecules to have ionizable carboxyl and amino groups in order to retain bioactivity. These ionizable groups limit the membrane permeability of RGD analogs and, thus, their oral bioactivity. (see Wang at pp. 437-438) Regarding simple alkyl monoester prodrugs, Wang states that masking of only the carboxyl group is often insufficient to improve oral activity because the ionizable amino group also contributed to the charge and polarity of the molecules and therefore low membrane permeability. (see Wang p.441) Wang thus suggests masking of more than one of the ionizable functional groups as a more effective strategy for improving the oral activity of RGD analogs than simply masking the free carboxyl group. (see Wang at pp. 442, 443)

Applicant respectfully reiterates that the objective of the present invention is to provide monoesters of (3*S*,4*aR*,6*R*,8*aR*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl]-1,2,3,4,4*a*,5,6,7,8,8*a*-decahydroisoquinoline-3-carboxylic acid. Notably, this carboxylic acid drug contains no less than three ionizable functional groups:



It is Applicant's view that one skilled in the art, in possession of the general teachings of Wang, would be without the requisite motivation to prepare simple alkyl monoesters that mask only the carboxyl functional group in favor of the double, triple and cyclic prodrug strategies also set forth in Wang. Furthermore, even if one skilled in the art were to pursue a simple alkyl monoester approach for improving the oral bioavailability of (3*S*,4*aR*,6*R*,8*aR*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl]-1,2,3,4,4*a*,5,6,7,8,8*a*-

decahydroisoquinoline-3-carboxylic acid, there would be no reasonable expectation of success in view of the remaining, unmasked ionizable functional groups which could negatively impact the membrane permeability of the resulting molecule, and thus its oral bioavailability.

Regarding Bundgaard II, also cited in the present Official Action, the motivation provided by this reference is even more tenuous. First, this reference is in the field of agents for ocular delivery. Further, unlike the present invention, the functional drug in this reference does not contain a free carboxylic acid group, but rather contains a cyclized lactone. The ester prodrugs that are disclosed in this reference are not merely metabolized to yield the active functional drug, but rather must first undergo cleavage of an alkyl ester moiety, followed by intramolecular cyclization to yield the active lactone. Considered as a whole, it is Applicant's view that Bundgaard II is not an analogous art reference relevant to the obviousness analysis of the simple alkyl monoesters of the type of the present invention.

In summary, the references cited in support of the present rejection under 35 USC §103(a) disclose a wide variety of ester prodrug approaches including aliphatic esters, aromatic esters, acyloxyalkyl double esters, alkoxycarbonyloxyalkyl double esters, double amidooxime ester prodrugs, double carbamoyl ethyl ester prodrugs, as well as triple prodrugs (acetate-carbamoyl-alkyl esters; carbamoyl-dialkyl esters; and hydroxyl-dialkyl esters) and coumarin based cyclic prodrugs. Regarding simple alkyl monoester prodrugs of the type of the present invention, however, the cited art, when taken as a whole, actually teaches away from such compounds in favor of highly functionalized esters, or double and triple prodrugs. Furthermore, to the extent that the cited references do in fact disclose simple alkyl monoesters, these disclosures nonetheless fail to provide the requisite expectation of success in obtaining a simple alkyl monoester that improves the bioavailability of (3*S*,4*aR*,6*R*,8*aR*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl]-1,2,3,4,4*a*,5,6,7,8,8*a*-decahydroisoquinoline-3-carboxylic acid.

In view of the discussion herein, Applicant respectfully submits that the bases for the rejection of the present claims under 35 U.S.C. §103(a) has been obviated. Applicant courteously requests withdrawal of the pending rejection under 35 U.S.C. §103(a), reconsideration of the claims, and passage of the present case to allowance. In the event that the Examiner intends to once again reject the present invention, or if verbal discussion would

be of any assistance in advancing prosecution of the present application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided.

Respectfully submitted,

/Alexander Wilson/

Alexander Wilson
Attorney for Applicant
Registration No. 45,782
Phone: 317-277-0190

Eli Lilly and Company
Patent Division/AW
P.O. Box 6288
Indianapolis, Indiana 46206-6288

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